ORIGINAL ARTICLE

Investigation of prophylactic effect of tranexamic acid in preventing postpartum hemorrhage in Besat Hospital in Sanandaj

FARIBA FARHADIFAR[1], SHOLE SHAHGHEIBI[2], SHAMSY ZARE[3], MASOUMEH REZAIE[3], FARIBA SEYEDOLSHOHADAE[3], SEYEDEH REYHANEH YOUSEFI SHARAMI[3], FATEME TAHMASEBI[3], MAHBOOBE KOOHESTANI[3], VIDA AGHAMIRI[4], MOHSEN SOHRABI[5], BIJAN NOURI[6], MARYAM MOUSAVI[3*]

[1]*Social Determinants of Health Research Center, Full professor, Department of Gynecology, Faculty of Medicine*

[2]*Professor of Obstetrics & Gynecology, Kurdistan University of Medical Sciences, Sanandaj, Iran*

[3]*Department of Obstetrics and Gynecology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran*

[4]*Faculty of Nursing and Midwifery, Kurdistan University of Medical sciences, Kurdistan, Iran*

[5]*Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran*

[6]*Assistant Professor of Biostatistics Social Determinants of Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran*

**Corresponding authors: Maryam Mousavi. Department of Obstetrics and Gynecology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran. Email: marymousavi61@gmail.com*

ABSTRACT

Introduction: Postpartum hemorrhage is one of the main causes of morbidity and mortality in pregnant mothers. Some studies have used tranexamic acid before delivery. This medication has been found to be useful in reducing postpartum hemorrhage. Therefore, the aim of this study was to investigate the effect of tranexamic acid before hemorrhage in mothers without risk factors.

Materials and Methods: This double-blind clinical trial study was conducted on 100 pregnant women admitted to the labor ward of Besat Hospital in Sanandaj during November 2020 to March 2021. Participants were randomly selected and divided into two groups of receiving tranexamic acid (intervention) and placebo (control). Finally, outcomes such as maternal age, gestational age, body mass index, postpartum hemorrhage, hemoglobin depletion, hematocrit depletion, thromboembolism and drug allergy were studied in both groups.

Results: Between the two groups, the rate of hemoglobin depletion, hematocrit depletion and postpartum hemorrhage in the group that received tranexamic acid in the active phase of labor was lower than the group that did not receive tranexamic acid (for all three cases P <0.001). Also, none of the patients developed thromboembolism and drug allergy following receiving tranexamic acid (P> 0.05).

Conclusion: During the active phase of labor, if tranexamic acid is prescribed to prevent severe postpartum hemorrhage, it can be effective in reducing postpartum hemorrhage.

Keywords: Tranexamic Acid, Postpartum Hemorrhage, Prophylaxis

INTRODUCTION

Primary postpartum hemorrhage (PPH) is one of the most common postpartum complications in both cesarean section and vaginal delivery and is the leading cause of maternal mortality worldwide [1]. According to the standard definition, PPH is a blood loss of 500 ml or more in the first 24 hours after childbirth, regardless of the mode of delivery [2]. This complication has led to the death of 21% of mothers in developing countries and 13% in developed countries [3]. The most common causes of postpartum hemorrhage are atony، birth canal injuries, retained placenta and coagulation disorders, and this increase in mortality can be due to various reasons, including increased age of pregnant mothers, increased number of cesarean sections, etc. [4]. Since the direct cause of PPH is poor uterine contractions, obstetric and uterine interventions and uterine medications are recommended, including prescription of oxytocin, misoprostol, and methergine [5, 6]. Recent studies have shown a tendency to investigate tranexamic acid (TA), but its effect has not yet been proven or rejected [7].

Recent studies have shown that antifibrinolytics such as TA can reduce fibrinolysis to prevent excessive blood loss during heart surgery, trauma, liver transplantation, etc. [8-10]. In addition, TA has been shown to be safe for clinical use during pregnancy and lactation [11]. Previous randomized clinical trials (RCTs) and meta-analyses have also shown that TA reduces blood loss during and after cesarean section [7, 12-15]. In addition to the beneficial effects of TA, contraindications to injectable and oral TA have also been reported, so that TA injection causes active intravascular clotting or subarachnoid hemorrhage, and oral administration can lead to thromboembolic diseases such as DVT and pulmonary embolism and a history of thrombosis or thromboembolism. Furthermore, it is necessary to rule out thrombogenic heart disease and not to take OCP at the same time. With these descriptions, theoretically, by prescribing this medication, fibrinolysis and more bleeding during childbirth can be prevented, and the prognosis of childbirth can be improved and maternal mortality can be reduced.

Therefore, in this study, given that bleeding is the most important cause of postpartum death in developing countries and also considering the importance of proper management of the third and fourth stages of delivery in preventing postpartum hemorrhage and atony of the uterus (as one of the important causes of it) we decided to investigate the prophylactic effect of tranexamic acid in preventing postpartum hemorrhage.

MATERIALS AND METHODS

Selection of patients: In this double-blind clinical trial study using EPITOOLS software, 100 nulliparous pregnant women admitted to Besat Hospital in Sanandaj for delivery during November 2020 to March 2021 were included in the study. All patients were mothers at gestational age from 38 weeks to 41 weeks and all mothers were nulliparous. Then, the samples were divided into 2 groups A (intervention) and B (control) by computer random selection. So that 50 pregnant women in the active phase of labor and at the time of complete dilatation who received tranexamic acid as group A and 50 women who received placebo as group B were investigated. Inclusion criteria were nulliparous and term of women. Exclusion criteria were multiparous women, pregnancies with preeclampsia, fetal growth restriction, and gestational diabetes.

Also, this study was conducted after obtaining a study permit from the Vice Chancellor for Research of Kurdistan University of Medical Sciences (RI.MUK.REC 1397.236) and registration in the clinical trial registry system (IRCT number: 2018.225042109n9). In addition, written consent was obtained from all patients to participate in this study and they were assured that their information would be kept confidential and that they would be provided with the results of the research if they wished. The samples were also reassured that they could leave the study at any stage of the research if they did not wish to continue.

Implementation method: Patients were injected with TA (Caspian Tamin, Iran) in the form of one gram per 100 cc of normal saline as an infusion in the active phase of labor at a rate of 10 cc per minute and were followed up for 48 hours after childbirth. The patients' blood samples were taken upon arrival and were considered as the first hematocrit and hemoglobin. In the active phase of labor in complete dilatation of the cervix, TA was administered as infusion into normal saline. Method of administration of TA was infused as one gram in 100 cc of normal saline at a rate of 10 cc per minute. Postpartum hemorrhage was considered to be 30 cc as the number of sterile gauzes of 10 in 10, each gauze completely stained to blood. The number of sterile gauzes was checked by number. During postpartum hospitalization, blood samples were taken again from all patients within 6 hours postpartum and were considered as postpartum hematocrit and hemoglobin. The difference between hemoglobin and hematocrit was obtained by comparing two hemoglobin and hematocrit in blood samples.

Finally, demographic variables such as maternal age, gestational age, body mass index and consequences such as postpartum hemorrhage, hemoglobin depletion, hematocrit depletion, thromboembolism and drug allergy were studied in two groups.

Statistical analysis: Statistical methods: STATA software version 12 was used to analyze the data. The assumption of normality of the data was checked using shapiro-wilk test. Comparison of normal variables in the two groups was performed using independent t-test and comparison of non-normal variables in the two groups was performed using Mann-Whitney unstable test. The significant level was considered to be 5%.

RESULTS

The present study was conducted on 100 term pregnant women who received tranexamic acid (intervention group) and placebo (control) during the active phase of labor. According to Table 1, demographic variables such as BMI, maternal age and gestational age at the end of pregnancy were investigated in the two groups and no significant difference was observed between the two groups in any of the mentioned variables (P> 0.05).

Table 1. Comparison of demographic factors in the two groups studied

Variables	Mean ± Std. Deviation		p-value
	Control	Intervention	
BMI	3/98 ± 25/80	4/56 ± 25/42	0/65
Maternal age	5/53 ± 25/34	5/01 ± 25/90	0/56
Gestational age at the end of pregnancy	0/51 ± 39/32	0/63 ± 39/38	0/84

Comparison of the difference between hemoglobin, hematocrit and prenatal and postpartum hemorrhage in the two groups showed that in the control group who did not receive tranexamic acid, the rate of hemoglobin, hematocrit and hemorrhage was higher than patients who received tranexamic acid during the active phase of labor and this difference was statistically significant in Mann-Whitney test (P=0.001 for all three cases) (Table 2).

Table 2. Comparison of hemoglobin, hematocrit and hemorrhage in the two groups

Variables	Mean ± Std. Deviation		p-value
	Control	Intervention	
Hemoglobin difference	1/40 ± 2/52	0/79 ± 1/13	0/001
Hematocrit difference	3/80 ± 7/04	3/11 ± 3/49	0/001
Hemorrhage	± 573/60 166/12	97/39 ± 300/80	0/001

Table 3 also showed that none of the patients developed thromboembolism and drug allergy after receiving tranexamic acid and according to Fisher's exact test, no significant difference was seen between the two groups (P=1.0).

Table 3. Comparison of thromboembolism and drug allergy in the two groups

Variables				p-value
		Control	Intervention	
Thromboembolism	Yes (N/%)	0	50/100	1/0
	No (N/%)	0	50/100	
Drug allergy	Yes (N/%)	0	50/100	1/0
	No (N/%)	0	50/100	

DISCUSSION

Research has shown that TA can reduce blood loss associated with complications such as placenta previa,

lower genital trauma as well as bleeding from the placenta. It has been reported that the use of TA can potentially prevent some cases of PPH. Slowly [8]. Therefore, it may be particularly helpful in preventing cases of PPH due to factors other than uterine atony, where uterine medications are not effective. The aim of this study was to determine the prophylactic effect of TA in preventing postpartum hemorrhage in Besat Hospital in Sanandaj.

The results of the present study showed a significant difference in hemoglobin, hematocrit and hemorrhage by comparing the two groups. Also, during the study, none of the patients developed thromboembolism and drug allergy following receiving TA.

Antifibrinolytics have been shown to be widely used during the early stages of postpartum hemorrhage due to the prevalence of hyperfibrinolysis and fibrinogen removal. Antifibrinolytics, especially TA, appear to be involved in reducing maternal hemorrhage and the need for blood transfusions. TA has an antifibrinolytic effect that blocks the lysine-binding sites of plasminogen, which prevents fibrin depletion. In addition, the use of TA in postpartum hemorrhage has been reported to have a 20% reduction in maternal mortality and a 30% reduction in the need for laparotomy [16]. Although TA is not specific for coagulopathies, its mechanism of performance can reduce the fibrinolysis process, thereby modulating bleeding and the consumption of coagulation factors [17]. In a study consistent with our findings, Xia et al. reported in a meta-analysis study that patients treated with TA had lower total and postoperative blood loss as well as lower incidence of PPH. However, according to their results, the incidence of nausea or vomiting was higher in the TA group [18]. In another study, Gungorduk et al., examining the effects of intravenous TA supplementation for active management of third stage of labor to reduce vaginal bleeding during the third and fourth stages of labor, showed that using TA and standard active management of third stage of labor reduced postpartum hemorrhage [12]. Sakun et al. also examined the effect of TA in preventing PPH after vaginal delivery in a random meta-analysis. Their results showed that women who received TA after vaginal delivery had significantly lower initial PPH and less hemorrhage. Also, the risk of thrombotic events was not increased in the group receiving TA [19]. On the other hand, in another meta-analysis study on the effect of using TA on the number of PPH, Li et al. stated that no final conclusion can be drawn regarding the effect of the abovementioned medication in vaginal delivery as the definition and criterion of obstetric hemorrhage vary in different areas, Which may increase the heterogeneity in the results [11].

Premature activation of fibrinolysis after trauma is common and is associated with increased mortality. Trauma activates the secretion of tissue plasminogen activator and the enzyme that converts plasminogen to plasmin fibrinolytic enzyme [20]. Rapid activation of fibrinolysis after delivery has been reported, and within one hour after delivery, the serum concentration of tissue plasminogen activator almost doubles, possibly due to tissue damage during labor, after which the concentration decreases. According to the results of studies conducted in surgeries, TA is used for the initial treatment of postpartum hemorrhage if uterotonics cannot control the bleeding or if it is possible that the hemorrhage is due to trauma [16]. Studies have shown that in healthy women with low risk of severe spontaneous vaginal postpartum, oxytocin combined with tranexamic acid caused a 60% reduction in primary postpartum hemorrhage [21]. 1 g (10 cc of solution) is injected within 10 to 20 minutes because infusion of more than 10 cc per minute causes a drop in blood pressure. In addition, the antifibrinolytic effect of TA has been shown to persist in serum for up to 7-8 hours. Because its concentration in breast milk is about 0.01 of the peak serum level of the mother's blood and it is unlikely for it to have an antifibrinolytic effect in the newborn [9].

Furthermore, research has shown that pregnancy is associated with an increased risk of deep vein thrombosis (DVT), which should be considered for any treatment that affects blood clotting [22]. Several studies have shown that administering TA during surgery, including for pregnant women, is safe [23-26]. In addition, physicians should be aware that TA can cause nausea and vomiting, and consider this when deciding whether or not to do this treatment. However, these side effects do not outweigh the potential benefits of reducing blood loss [18].

However, the present study had limitations such as the refusal of some clients to enter the study and the limited number of patients. Also, it is suggested that in future studies, the consequences of pregnancy after injection of TA in other phases of labor in pregnant women, the effect of TA in controlling late postpartum hemorrhage and its effect on pregnancy consequences orally.

CONCLUSION

According to the results of this study, prophylactic infusion of tranexamic acid in the active phase of labor can be effective in reducing postpartum hemorrhage.

REFERENCES

1. Driessen M, Bouvier-Colle MH, Dupont C, Khoshnood B, Rudigoz RC, Deneux-Tharaux C. Postpartum hemorrhage resulting from uterine atony after vaginal delivery: factors associated with severity. Obstet Gynecol. 2011;117(1):21-31. doi:10.1097/AOG.0b013e318202c845.
2. Sentilhes L, Merlot B, Madar H, Sztark F, Brun S, Deneux-Tharaux C. Postpartum haemorrhage: prevention and treatment. Expert Rev Hematol. 2016;9(11):1043-1061. doi:10.1080/17474086.2016.1245135.
3. Ghalandari S, Kariman N, Sheikhan Z, Shahrahmani H, Asadi N. Systematic review on variety of effective treatment methods for postpartum hemorrhage in Iran and world. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2016;19(15):16-38.
4. Saccone G, Migliorini S, Crocetto F, Della Corte L, Cancellieri E, Improda L, Improda FP, Maruotti GM, Cancelmo G, Imbimbo C, et al. Risk of unscheduled delivery in women with placenta accreta according to planned gestational age at delivery. J Matern Fetal Neonatal Med. 2021:1-4. doi:10.1080/14767058.2021.1878493.
5. Al Wattar BH, Tamblyn JA, Parry-Smith W, Prior M, Van Der Nelson H. Management of obstetric postpartum hemorrhage: a national service evaluation of current practice in the UK. Risk Manag Healthc Policy. 2017;10:1-6. doi:10.2147/rmhp.s121737.
6. Lotfalizadeh M, Mansouri A, Mansouri M, Ghomian N. Evaluation of Causes and Therapeutic Methods of Controlling of Postpartum Hemorrhage in two Governmental

Hospital of Mashhad, Iran. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2013;16(62):1-5.
7. Sentilhes L, Winer N, Azria E, Sénat MV, Le Ray C, Vardon D, Perrotin F, Desbrière R, Fuchs F, Kayem G, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018;379(8):731-742. doi:10.1056/NEJMoa1800942.
8. Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. Expert Opin Pharmacother. 2011;12(4):503-516. doi:10.1517/14656566.2011.545818.
9. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2015(6):Cd007872. doi:10.1002/14651858.CD007872.pub3.
10. Pacheco LD, Saade GR, Hankins GDV. Medical management of postpartum hemorrhage: An update. Semin Perinatol. 2019;43(1):22-26. doi:10.1053/j.semperi.2018.11.005.
11. Li C, Gong Y, Dong L, Xie B, Dai Z. Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention?: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(1):e5653. doi:10.1097/md.0000000000005653.
12. Gungorduk K, Asıcıoğlu O, Yıldırım G, Ark C, Tekirdağ A, Besımoglu B. Can intravenous injection of tranexamic acid be used in routine practice with active management of the third stage of labor in vaginal delivery? A randomized controlled study. Am J Perinatol. 2013;30(5):407-413. doi:10.1055/s-0032-1326986.
13. Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, Shirdel M. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. Aust N Z J Obstet Gynaecol. 2015;55(1):53-58. doi:10.1111/ajo.12262.
14. Sharafi A, Ghasemi M. Comparison of rectal misoprostol's effect when used before and after a cesarean section on post-cesarean bleeding. Journal of gynecology obstetrics and human reproduction. 2019;48(2):129-132.
15. Sarvi F, Alleyassin A, Aghahosseini M, Ghasemi M, Gity S. Hysteroscopy: A necessary method for detecting uterine pathologies in post-menopausal women with abnormal uterine bleeding or increased endometrial thickness. Turkish journal of obstetrics and gynecology. 2016;13(4):183.
16. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105-2116. doi:10.1016/s0140-6736(17)30638-4.
17. Edlund M. Nonhormonal treatments for heavy menstrual bleeding. J Womens Health (Larchmt). 2011;20(11):1645-1653. doi:10.1089/jwh.2010.2696.
18. Xia Y, Griffiths BB, Xue Q. Tranexamic acid for postpartum hemorrhage prevention in vaginal delivery: A meta-analysis. Medicine (Baltimore). 2020;99(3):e18792. doi:10.1097/md.0000000000018792.
19. Saccone G, Della Corte L, D'Alessandro P, Ardino B, Carbone L, Raffone A, Guida M, Locci M, Zullo F, Berghella V. Prophylactic use of tranexamic acid after vaginal delivery reduces the risk of primary postpartum hemorrhage. J Matern Fetal Neonatal Med. 2020;33(19):3368-3376. doi:10.1080/14767058.2019.1571576.
20. Tsai SJ. Role of tissue-type plasminogen activator and plasminogen activator inhibitor-1 in psychological stress and depression. Oncotarget. 2017;8(68):113258-113268. doi:10.18632/oncotarget.19935.
21. Muñoz M, Stensballe J, Ducloy-Bouthors AS, Bonnet MP, De Robertis E, Fornet I, Goffinet F, Hofer S, Holzgreve W, Manrique S, et al. Patient blood management in obstetrics: prevention and treatment of postpartum haemorrhage. A NATA consensus statement. Blood Transfus. 2019;17(2):112-136. doi:10.2450/2019.0245-18.
22. AbouZahr C. Global burden of maternal death and disability. Br Med Bull. 2003;67:1-11. doi:10.1093/bmb/ldg015.
23. Abdel-Aleem H, Alhusaini TK, Abdel-Aleem MA, Menoufy M, Gülmezoglu AM. Effectiveness of tranexamic acid on blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Fetal Neonatal Med. 2013;26(17):1705-1709. doi:10.3109/14767058.2013.794210.
24. Cheriyan T, Maier SP, 2nd, Bianco K, Slobodyanyuk K, Rattenni RN, Lafage V, Schwab FJ, Lonner BS, Errico TJ. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. Spine J. 2015;15(4):752-761. doi:10.1016/j.spinee.2015.01.013.
25. Sahhaf F, Abbasalizadeh S, Ghojazadeh M, Velayati A, Khandanloo R, Saleh P, Piri R, Naghavi-Behzad M. Comparison effect of intravenous tranexamic acid and misoprostol for postpartum haemorrhage. Niger Med J. 2014;55(4):348-353. doi:10.4103/0300-1652.137228.
26. Shaaban MM, Ahmed MR, Farhan RE, Dardeer HH. Efficacy of Tranexamic Acid on Myomectomy-Associated Blood Loss in Patients With Multiple Myomas: A Randomized Controlled Clinical Trial. Reprod Sci. 2016;23(7):908-912. doi:10.1177/1933719115623646.